Cancer Investigation, 7(3), 267-276 (1989)

CONTROVERSIES IN BASIC SCIENCE

The Question of Thresholds for Radiation and Chemical Carcinogenesis

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INTRODUCTION

Selection of the dose-incidence model that is appropriate for predicting the risks of cancer from low-level exposure to a given carcinogen is among the most contentious issues in public health. Although the existence of a threshold in the dose-effect relationship is well documented for many, if not most, types of toxicological effects, the existence of a threshold for the mutagenic effects of ionizing radiation (1-3) and of certain chemicals (4,5) has been questioned since the middle of the century. More recently, the existence of a threshold for carcinogenic effects also has been seriously questioned, since carcinogenesis may, likewise, be envisioned to result from effects on individual cells rather than groups of cells (6-8).

Because in principle it is not possible to prove or disprove the existence of a threshold for carcinogenesis, the argument for or against the threshold hypothesis must be based on theoretical as well as empirical evidence (7,8). Some of the cogent data and concepts are surveyed in the following.

BIOLOGY OF CARCINOGENESIS

Monoclonal, Multicausal, Multistage Nature of Cancer

The evidence that cancer usually originates from a single transformed cell (9-11) implies that appropriate damage to one cell alone may suffice to increase the probability of neoplasia in a suitably susceptible individual. A single alteration, however, apparently does not suffice to convert a normal cell into a cancer cell. On the contrary, cancer typically appears to evolve through a succession of stages; for example, initiation, promotion, and progression (12,13).

The mechanism of *initiation* remains to be established, but some type of mutational change is implicated by evidence that: (i) the initiating event is relatively prompt and irreversible (14,15); (ii) most ultimate carcinogens are mutagens (16); (iii) the frequency of cell transformation that is induced by a given carcinogen is usually maximal if exposure to the agent occurs just before or during

DNA synthesis (17); (iv) the carcinogenic potency of an initiating chemical is generally correlated with the extent to which it binds covalently to DNA and with the nature of the resulting DNA adducts; and (v) DNA to which a chemical carcinogen is bound can serve as a template for DNA replication (18) which, along with subsequent cell division, is necessary to "fix" the potential for neoplastic change (19); (vi) susceptibility to cancer is increased in persons who are deficient in their capacity to repair DNA damage (20). Whatever the nature of the mutational change may be, it results in a frequency of initiation that is orders of magnitude higher than the rate of mutations at any given gene locus (21,22), implying that multiple oncogenic sites, damage to the genome at sites unlikely to be repaired (e.g., tandem repeats), or genetic damage other than point mutations are likely to be involved (14).

The specific genes that are affected may be presumed to include antioncogenes as well as oncogenes (Table 1). Initiation can thus be envisioned to result either from the homozygous inactivation or deletion of an antioncogene, or from the aberrant activation of an otherwise normal proto-oncogene, through aneuploidy, chromosomal rearrangement, or point mutation. For neoplastic transformation, as opposed to initiation, the activation of a single oncogene alone appears to be insufficient (13).

Although initiation can result from only one exposure to an appropriate initiating agent, tumor *promotion* typically requires repeated and sustained exposures to an appropriate promoting agent, although low doses of the agent may suffice. In two-stage mouse skin carcinogenesis, for example, nanomolar concentrations of 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) are sufficient to promote the effects of radiation or chemical initiators, causing concomitant stimulation of: (i) macromolecular synthesis; (ii) hyperplasia; (iii) polyamine synthesis; (iv) prostaglandin synthesis; (v) protease production; (vi) alterations of certain cell membrane enzymes and glycoproteins; (vii) induction of sister-chromatid exchanges; (viii) altered differentiation; and (ix) modified responses to various growth-controlling factors (23). Whether any one of these changes is critical for tumor promotion, however, is not clear. Traditionally, TPA and other tumor-promoting agents have been considered to act predominantly through epigenetic mechanisms (24,25), but recent observations indicate that some of these agents can damage DNA indirectly (26–29) implying that such genotoxic effects also may be involved in promotion.

Tumor *progression*, the process through which successive generations of neoplastic cells give rise to increasingly autonomous clonal derivatives (30), has been attributed at least in part to mutations and chromosome aberrations (15). The process can be accelerated, however, by selection pressures that favor the outgrowth of proliferative subpopulations, including repeated exposure to growth-stimulating agents and carcinogens (15,30).

Table 1

Comparative Properties of Oncogenes and Antioncogenes

Oncogenes	Antioncogenes
Gene active	Gene inactive
Specific translocations	Deletions or invisible mutations
Translocations not hereditary	Mutations hereditary and nonhereditary
Dominant	Recessive
Tissue specificity may be broad	Considerable tissue specificity
Especially leukemias and lymphomas	Solid tumors (e.g., Wilm's, retinoblastoma)

Source: From Ref. 20.

EMPIRICAL DOSE-INCIDENCE RELATIONSHIPS FOR CARCINOGENSIS

Although hundreds of chemicals have been found to be oncogenic in laboratory animals, less than three dozen have been observed to be capable of inducing cancer in humans (31). With few exceptions, moreover, the relevant data are not sufficient to characterize the dose-incidence relationship except in a semiquantitative way (8).

With ionizing radiation, for which the dosimetry is less complicated by pharmacokinetic variables than is the dosimetry for most chemicals, dose-incidence data are available over a relatively wide range of radiation doses (32,33). At best, however, the data do not suffice to define the dose-incidence relationship in the low-dose domain. Assessment of the carcinogenic risks associated with low-level irradiation must thus depend on extrapolation from observations at higher levels of exposure, based on assumptions about the relevant dose–incidence relationships and mechanisms of carcinogenesis.

The extrapolation models that are used for estimating the carcinogenic risks of low-level irradiation generally assume a linear nonthreshold relationship between risk and dose in the low-dose domain, although the data do not exclude a threshold (8,33,34). Among the lines of epidemiological evidence that are consistent with a

nonthrehsold relationship are: (i) a 25–50% excess of leukemia in children exposed to diagnostic x-rays in utero, in whom the radiation dose is estimated to have averaged less than 50 mGy (35,36); (ii) an excess of thyroid tumors in persons who received therapeutic irradiation of the scalp in childhood for tinea capitis, in whom the dose to the thyroid gland is estimated to have averaged no more than 60–80 mGy (37,38); (iii) a dose-dependent excess of breast cancer, of essentially the same magnitude for a given dose, in: (a) women exposed to A bomb radiation, (b) women given therapeutic irradiation of the breast for postpartum mastitis, (c) women who received multiple fluoroscopic examinations of the chest during the treatment of pulmonary tuberculosis with artificial pneumothorax, and (d) women exposed to external gamma radiation in the painting of luminous clock and instrument dials (33,39); and (iv) a dose-dependent excess of leukemia in A bomb survivors, which is evident at doses below 300 mGy (33,34). In each of the above populations, the dose-incidence data in low-to-intermediate dose range are compatible with a linear nonthreshold relationship for the neoplasms in question. Comparable data, moreover, are available for certain radiation-induced neoplasms in laboratory animals (8,32,40,41). As concerns the carcinogenic effects of chemicals, quantitative dose–incidence data for humans are extremely limited, with few exceptions. A noteworthy exception is cigarette smoke, the major cause of lung cancer. In cigarette smokers, the incidence of lung cancer increases as a function of the number of cigarettes smoked per day raised approximately to a power of 1.8 (42). Furthermore, the absence of any clear indication of a threshold in the dose–incidence curve

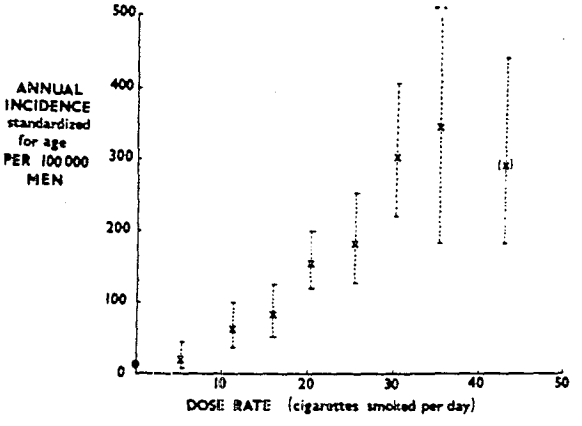

Figure 1. Annual incidence of lung cancer in regular cigarette smokers, in relation to the number of cigarettes smoked per day. (From Ref. 61.)

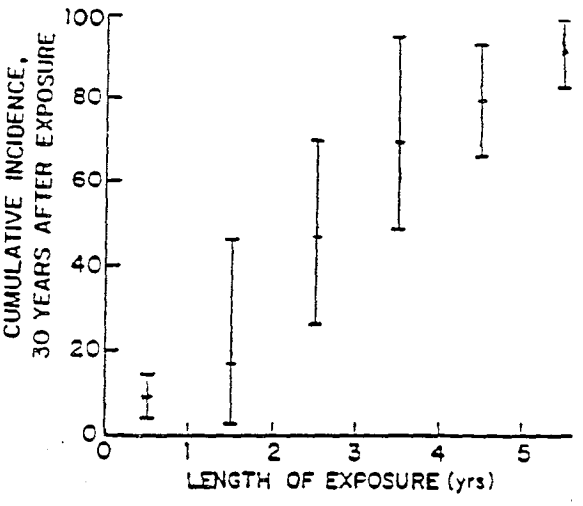

Figure 2. Cumulative incidence of cancer of the urinary bladder in 78 distillers of β-naphthylamine and benzidine. (From Ref. 8, based on data from Ref. 62.)

(Fig. 1) is consistent with epidemiological data implying that the risk of lung cancer can be increased even in nonsmokers by passive exposure to cigarette smoke over prolonged periods (43).

Other populations for which the dose–incidence data are compatible with a nonthreshold type of response include groups of chemists who were employed as distillers of 2-naphthylamine. In one such group, the cumulative incidence of cancer of the urinary bladder was observed to increase with the duration of occupational exposure, approaching 100% in workers who were exposed for five years or longer (Fig. 2).

In asbestos workers, likewise, the rates of lung cancer and mesothelioma appear to increase linearly with the intensity and duration of exposure (44). Furthermore, in asbestos workers who smoke cigarettes, the combined carcinogenic effects of asbestos and cigarette smoke appear to be multiplicative rather than merely additive (Table 2), implying that the two agents exert their effects through complementary rather than similar mechanisms.

With respect to the mechanism of cigarette smoke-induced carcinogenesis, it is noteworthy that the excess of lung cancer in ex-smokers stops rising relatively promptly after cessation of smoking (45), suggesting that cigarette smoke affects primarily late stages of carcinogenesis. The carcinogenic effects of cigarettes thus stand in contrast to those of radiation (33) and asbestos (46), which continue to become manifest for decades after exposure.

Table 2

Age-Standardized Lung Cancer Death Rates as Affected by Cigarette Smoking, Occupational Exposure to Asbestos Dust, or Both[a]

Exposure to asbestos	History of cigarette smoking	Death rate	Mortality difference	Mortality ratio
No	No	11.3	0.0	1.00
Yes	No	58.4	+47.1	5.17
No	Yes	122.6	+111.3	10.85
Yes	Yes	601.6	+590.3	53.24

[a]Age-standardized lung cancer death rates are rates per 100,000 man-years standardized for age on the distribution of the man-years of all the asbestos workers. Number of lung cancer deaths based on death certificate information.

Source: From Ref. 59.

Because of the multicausal, multistage nature of carcinogenesis and the fact that the mechanism of carcinogenesis is not the same for all cancers and all agents, some diversity of dose–incidence relationships is to be expected. The neoplasms that are induced by a given chemical in different tissues or in animals of different species also may vary in dose–incidence relationships because of pharmacogenetic and pharmacokinetic differences affecting the dosage of carcinogen to different target cells (47). The observed age- and tissue-dependent variations in dose–incidence relationships among radiation-induced neoplasms are largely unexplained as yet (41), but differences in cell proliferation kinetics and homeostatic ability (including capacity to repair DNA damage) may constitute potential sources of such variation (20).

To explore the dose–incidence curve for carcinogenesis at low doses, a number of large-scale experiments have been carried out with laboratory animals. In the largest of these to date, the incidence of hepatomas in mice was observed to increase with the concentration of 2-AAF in the diet even at the lowest dose level tested (Fig. 3), whereas the dose–incidence curve for tumors of the urinary bladder was quasithresholded (Fig. 3). This contrast in dose–incidence curves may have resulted from differences between the liver and the bladder in the metabolism of 2-AAF among other explanations.

Because a given carcinogen may influence the probability of neoplasia through more than one type of effect, at least at high dose levels, its dose–incidence curve can reflect differing combinations of initiating effects, promoting effects, and anticarcinogenic effects, depending on the dose and other circumstances. The combined effects of multiple agents may, likewise, be additive, synergistic, or antagonistic, depending on the agents in question and the conditions of exposure. At low to moderate dose levels, the effects of a complete carcinogen can generally be accentuated by appropriate tumor-promoting stimuli, which unmask initiating effects that would otherwise remain unexpressed (Fig. 4). It is noteworthy, moreover, that under conditions in which initiating effects are promoted to full expression they often increase as a linear nonthreshold function of the dose of the initiating agent (Fig. 4). Furthermore, whereas the carcinogenic effectiveness per unit dose of x-rays and gamma rays tends to

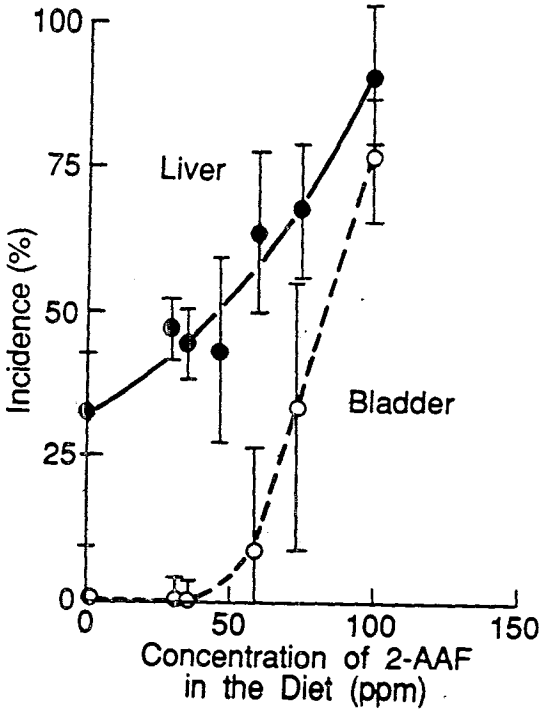

Figure 3. Cumulative incidence of tumors of the liver and of the urinary bladder in female BALB/c mice exposed to 2-acetylaminofluorene (2-AAF) at various concentrations in the diet for up to 33 months. (From Ref. 63.).

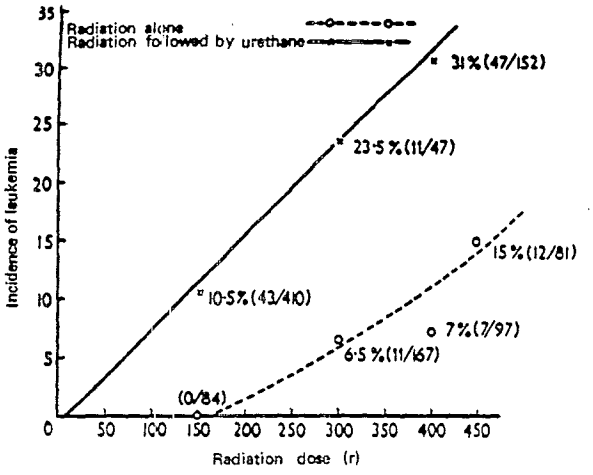

Figure 4a. Cumulative incidence (in percent) of leukemia in C57BL mice in relation to the dose of whole-body x-radiation administered in a single exposure (-o-o-), with or without subsequent injections of urethane (-x-x-). (Reproduced from Ref. 64.)

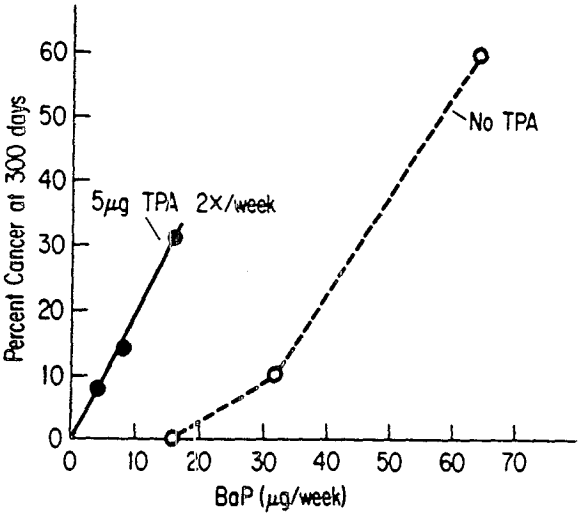

Figure 4b. Cumulative incidence of carcinomas of the skin in mice exposed once weekly to benzo(a)pyrene (BaP), with or without subsequent exposure to 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) twice weekly. Doses refer to the amount of B(a)P applied to the skin each week. (Reproduced from Ref. 65.)

decrease with decreasing dose and dose rate, that of high-LET radiation tends to remain constant or even increase (Fig. 5) (32,40,41).

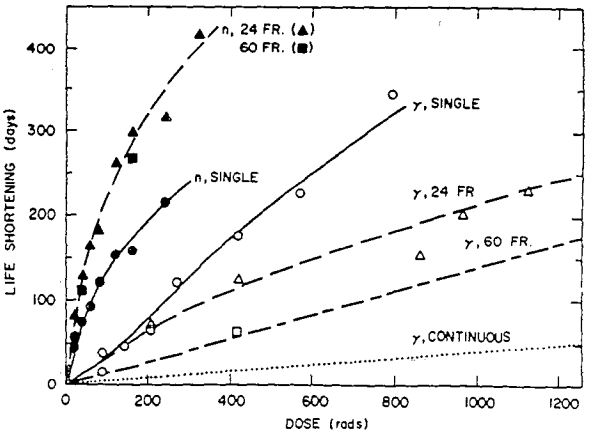

Figure 5. Life shortening (all causes) in male B6CF$_1$ mice in relation to the total dose of single, fractionated (FR), or continuous whole-body neutron- or gamma-irradiation. (Reproduced from Ref. 66.)

Cell Transformation In Vitro

The neoplastic transformation of cells in vitro, although not strictly analogous to carcinogenesis in vivo, provides a model system that can be helpful in identifying carcinogenic agents and exploring their mechanisms of action. Few detailed dose–response curves for cell transformation have been published as yet, but the morphological transformaton of Syrian hamster embryo cells by benzo(a)pyrene (BAP) (48,49) is consistent with one-hit kinetics except at cytotoxic dose levels (50). A one-hit model also holds for the transformation of such cells by the combined effects of x-rays and BAP (50). With x-rays alone, the frequency of transformation per surviving cell is increased by a dose as low as 10 mGy, above which it appears to increase curvilinearly with the dose up to 1.5 Gy; however, a linear increase over the same dose range cannot be excluded (51). Although the rate of transformation per unit dose typically decreases on protraction or fractionation of exposure to gamma rays, it may increase on protraction or fractionation of exposure to fast neutrons (Fig. 6).

In C3H101/2 cells irradiated in vitro—as well as in thyroid and mammary "clonogens" irradiated in vivo (52)—"initiation" appears to occur with a frequency as high as 0.01–0.1 per cell per Gy (53) and to increase as a linear nonthreshold function of the dose (Fig. 7). The subsequent, final transforming event in such cells is far rarer, however, occurring at a rate of only 10^{-6} to 10^{-7} per cell generation (53,54).

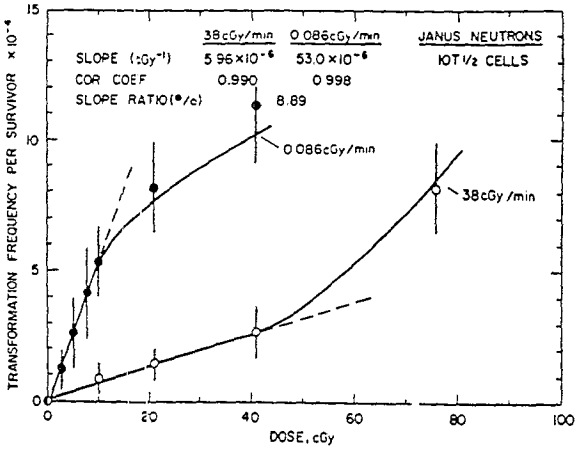

Figure 6. Frequency of neoplastic transformation in C3H 10T1/2 cells exposed to fission-spectrum neutrons. Dashed lines indicate linear regressions fitted to the initial portions of the dose-effect curves. (Reproduced from Ref. 67.)

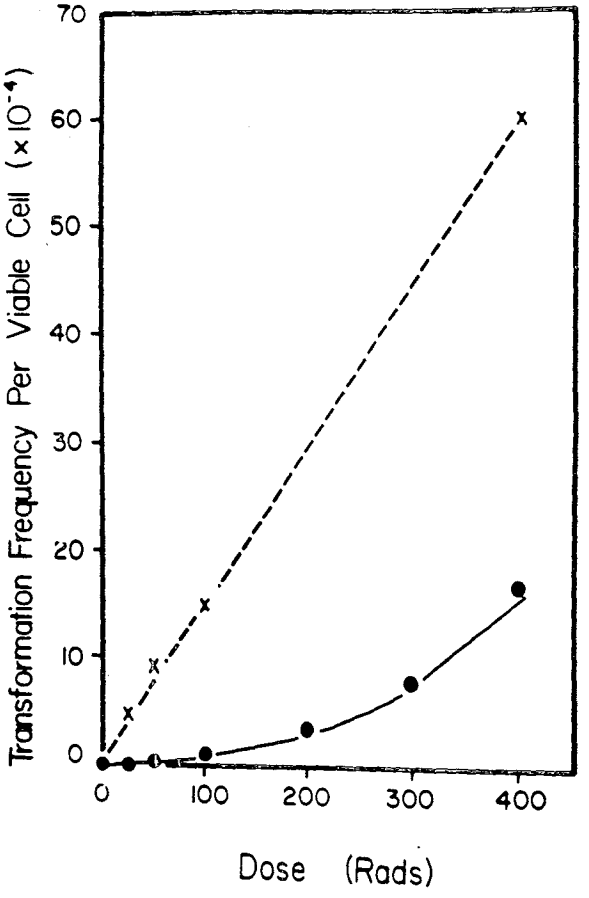

Figure 7. Dose-response relationship for the induction of neoplastic transformation in mouse 10T1/2 cells by x-rays alone (o), or by x-rays followed by phorbol ester, starting 48 h after irradiation and continued for the full 6-week expression period (•). No increase in transformation frequency was detected following exposure to phorbol ester alone. (Reproduced from Ref. 68.)

Interpolation and Extrapolation Models

Although the relation between the incidence of neoplasia and the dose of carcinogen is known to vary with the type of neoplasm, the carcinogen, and other variables, the dose-incidence relationships at low doses is not known precisely for any neoplasm or carcinogen. The risks of low-level exposure to a cancer-causing agent can thus be assessed only through interpolation or extrapolation from effects observed at higher levels of exposure. For many of the neoplasms induced by ionizing radiation, the dose-incidence relation generally conforms to the patterns illustrated in Figure 8, which are consistent with those to be expected if the probability of carcinogenesis could be increased in a suitably susceptible individual by an appropriate mutation or chromosomal aberration in a single somatic cell. Under this assumption, the dose–incidence curve for high-LET radiation would be expected to conform, in general, to the expression:

$$I = C + aD \qquad (1)$$

where I is the incidence at dose D, C is the incidence in nonirradiated controls, and the coefficient a is a constant; similarly, for low-LET radiation, the dose-incidence curve would conform, in general, to the expression:

$$I = (C + aD + bD^2)e^{-(pD+qD^2)} \qquad (2)$$

where the symobls are comparable to those above, except for a different value of the coefficient a and the addition of the coefficients b, p, and q (55).

While many of the observed dose-incidence curves conform to the latter pattern, the curve for radiation-induced breast cancer appears more nearly linear, as noted above. To allow for uncertainty about the shape of the dose-incidence curve at low doses and thus to obtain a range of reasonable risk estimates, alternative models (Figs. 9 and 10) have been used in assessing the risks of low-level exposure to carcinogens. Most such models treat carcinogenesis as a multicausal, multistage process. Depending on the particular model that is used for interpolation or extrapolation, however, the estimated risk at low doses can vary by order of magnitude (e.g., Table 3). The linear (one-hit) model for interpolating between the lowest dose

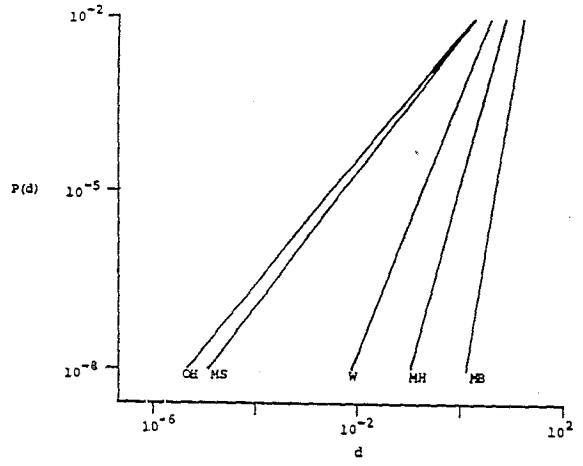

Figure 8. Estimated risk of liver cancer, p(d), in relation to the dose of aflatoxin, d, as determined with different dose-incidence models; i.e., OH, one-hit model; MS, multistage model; W, Weibull model; MH multihit model; and MB, Mantel-Bryan (log-probit model). (From Ref. 56.)

Table 3

Estimated Risk of Cancer of the Human Urinary Bladder from Daily Ingestion of 0.12 g of Saccharin

Method of transspecies scaling and of high- to low-dose extrapolation	Lifetime cases per million exposed
Rat dose adjusted to human dose by surface area rule	
Single-hit model	1,200
Multistage model (with quadratic term)	5
Multihit model	0.001
Mantel-Bryan probit model	450
Rat dose adjusted to human dose by mg/kg/day equivalence	
Single-hit model	210
Multihit model	0.001
Mantel-Bryan probit model	21
Rat dose adjusted to human dose by mg/kg/lifetime equivalence	
Single-hit model	5,200
Multihit model	0.001
Mantel-Bryan probit model	4,200

Source: From Ref. 60.

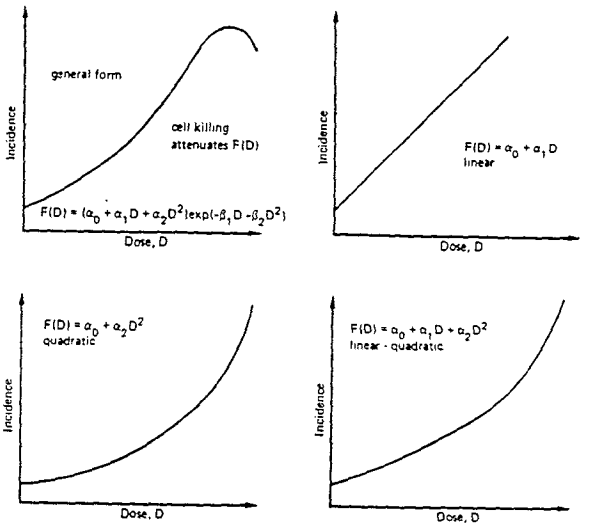

Figure 9. Dose-response curves for four different mathematical models relating cancer incidence to radiation dose which were evaluated by the National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiation. (From Ref. 33.)

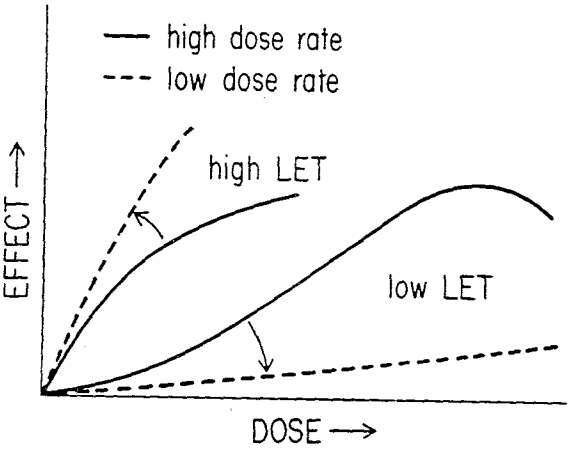

Figure 10. Diagrammatic representation of characteristic dose-response curves, relating the incidence of tumors in laboratory animals to the dose and dose rate of high-LET (——) radiation and low-LET (---) radiation. (Reproduced from Ref. 69.)

at which a significantly increased incidence has been observed and the baseline (zero dose) incidence is generally thought to overestimate the risk at low doses (8,56), and thus to provide an "upper limit" estimate of risk, with the lower limit of the range extending to zero.

Although the mechanisms of action of carcinogens of different types are still to be defined precisely, the existing data suggest that a linear nonthreshold interpolation model may be appropriate only for an initiating agent or a complete carcinogen, and that a model yielding a smaller estimate of the risk at low doses is more likely to be appropriate for a promoting agent. Similarly, for a chemical that is activated through nonlinear metabolic processes (57) or that acts through toxic effects elicited only at relatively high doses (e.g., immunosuppression) (58), a threshold or quasithreshold dose-incidence model is likely to be more appropriate.

In view, however, of the existence within the human population of individuals who vary widely in their susceptibility to cancer, as well as those who are at different stages of carcingenesis as a result of the action of other cancer-causing agents or risk factors, it is assumed that a carcinogen may pose some degree of risk to the population at any dose, by exerting carcinogenic effects that are additive with those which account for the "spontaneous" baseline incidence of cancer (Fig. 11). Hence, unless an agent can be shown to act through effects that are not additive with those which account for the "spontaneous" baseline incidence of cancer, a nonthreshold model is generally recommended for assessing the carcinogenic risks of the agent for public health purposes.

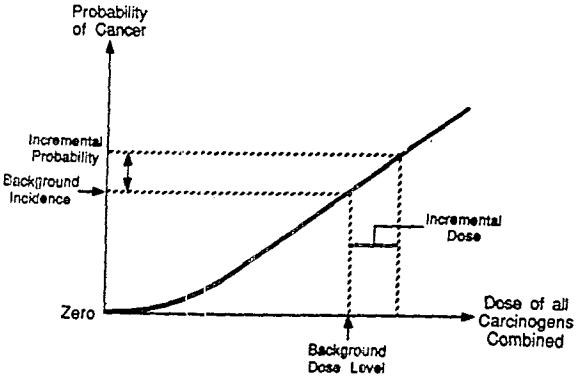

Figure 11. Diagram illustrating the expected increment in risk of cancer resulting from a low dose of a hypothetical carcinogen. Because cellular effects similar to those of the carcinogen may be produced in its absence by "background" mechanisms, the effects resulting from low doses of that carcinogen may be additive with those resulting from other "background" risk factors, thus causing an increase in the risk that is proportional to the dose. (From Ref. 70.)

ACKNOWLEDGMENT

Preparation of this report was supported in part by Grants ES 00260 and CA 13343 from the U.S. Public Health Service and Grant SIG-9 from the American Cancer Society.

The author is grateful to Mrs. Lynda Witte for assistance in the preparation of this report.

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